Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial

Marvin A Konstam, James D Neaton, Kenneth Dickstein, Helmut Drexler, Michel Komajda, Felipe A Martinez, Gunter A J Riegger, William Malbecq, Ronald D Smith, Soneil Guptha, Philip A Poole-Wilson,† for the HEAAL Investigators‡*

Lancet 2009; 374: 1840–48

Published Online November 17, 2009 DOI:10.1016/S0140-6736(09)61913-9

See Comment page 1808

Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA (Prof M A Konstam MD); **University of Minnesota, School of Public Health, Minneapolis, MN, USA** (Prof J D Neaton PhD); **Stavanger University Hospital, Stavanger, Norway** (Prof K Dickstein MD); **Institute of Internal Medicine, University of Bergen, Bergen, Norway** (Prof K Dickstein); **Medizinische Hochschule, Hannover, Germany** (Prof H Drexler MD); **Université Pierre et Marie Curie-Paris 6, Pitié-Salpêtrière Hospital, Paris, France** (Prof M Komajda MD); **Córdoba National University, Rusculleda Foundation for Clinical Research, Córdoba, Argentina** (Prof F A Martinez MD); **University Hospital Regensburg, Regensburg, Germany** (Prof G A J Riegger MD); **MSD-Europe, Brussels, Belgium** (W Malbecq PhD); **Merck & Co, Whitehouse Station, NJ, USA** (R D Smith PhD, S Guptha MD); **and National Heart and Lung Institute, Imperial College London, London, UK** (Prof P A Poole-Wilson MD)

*Prof H Drexler died September, 2009

†Prof P A Poole-Wilson died March, 2009

‡Investigators listed at end of paper

Correspondence to: Prof Marvin A Konstam, Tufts Medical Center, Box 108, 800 Washington Street, Boston, MA 02111, USA **mkonstam@tuftsmedicalcenter.org**

Summary

Background Angiotensin-receptor blockers (ARBs) are effective treatments for patients with heart failure, but the relation between dose and clinical outcomes has not been explored. We compared the effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure.

Methods This double-blind trial was undertaken in 255 sites in 30 countries. 3846 patients with heart failure of New York Heart Association class II–IV, left-ventricular ejection fraction 40% or less, and intolerance to angiotensin-converting-enzyme (ACE) inhibitors were randomly assigned to losartan 150 mg (n=1927) or 50 mg daily (n=1919). Allocation was by block randomisation stratified by centre and presence or absence of β-blocker therapy, and all patients and investigators were masked to assignment. The primary endpoint was death or admission for heart failure. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00090259.

Findings Six patients in each group were excluded because of poor data quality. With 4·7-year median follow-up in each group (IQR 3·7–5·5 for losartan 150 mg; 3·4–5·5 for losartan 50 mg), 828 (43%) patients in the 150 mg group versus 889 (46%) in the 50 mg group died or were admitted for heart failure (hazard ratio [HR] 0·90, 95% CI 0·82–0·99; p=0·027). For the two primary endpoint components, 635 patients in the 150 mg group versus 665 in the 50 mg group died (HR 0·94, 95% CI 0·84–1·04; p=0·24), and 450 versus 503 patients were admitted for heart failure (0·87, 0·76–0·98; p=0·025). Renal impairment (n=454 *vs* 317), hypotension (203 *vs* 145), and hyperkalaemia (195 *vs* 131) were more common in the 150 mg group than in the 50 mg group, but these adverse events did not lead to significantly more treatment discontinuations in the 150 mg group.

Interpretation Losartan 150 mg daily reduced the rate of death or admission for heart failure in patients with heart failure, reduced left-ventricular ejection fraction, and intolerance to ACE inhibitors compared with losartan 50 mg daily. These findings show the value of up-titrating ARB doses to confer clinical benefit.

Funding Merck (USA).

Introduction

Clinical trials have shown that angiotensin-receptor blockers (ARBs), given with or without an angiotensin-converting-enzyme (ACE) inhibitor, reduce morbidity or mortality in patients with heart failure and reduced left-ventricular ejection fraction (LVEF).[1–6] These trials investigated the effects of one high dose of an ARB and therefore do not provide guidance about optimum dosing or the relative risk–benefit profile of various dosing regimens.

Higher doses of ARBs than are typically used to treat hypertension could improve clinical outcomes in patients with heart failure. Trials establishing ARB efficacy have used valsartan 320 mg daily or candesartan 32 mg daily.[1–3] However, losartan 50 mg daily did not improve clinical outcomes compared with captopril 150 mg daily.[7] Incremental losartan doses of up to 150 mg in patients with heart failure result in progressive increases in plasma renin activity and in circulating concentrations of angiotensin II.[8] Taken together, these observations lend support to the possibility that high ARB doses could achieve improved clinical benefits, through more complete inhibition of angiotensin effects at the AT_1 receptor or increased stimulation of the AT_2 receptor.[9]

The Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study compared clinical outcomes in patients with heart failure, reduced LVEF, and intolerance to ACE inhibitors who were randomly assigned to a high (150 mg) or low (50 mg) daily dose of losartan. We tested the hypothesis that incremental losartan dosing would reduce the risk of the primary combined endpoint of death or admission for heart failure.

Methods

Study design and participants

The design of the study has been previously described.[10] HEAAL was an international, multicentre, double-blind, event-driven trial, comparing the effect of two doses of

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

SHOUT
SHARE
IT

losartan (Merck, Whitehouse Station, NJ, USA), 150 mg daily and 50 mg daily, on death or admission for heart failure. Patients were enrolled in this study between November, 2001, and March, 2005, at 255 sites in 30 countries.

Eligibility criteria for patients were: age 18 years or older; symptomatic heart failure (New York Heart Association [NYHA] class II–IV); LVEF 40% or less, with stable cardiovascular medical therapy for at least 2 weeks; and known intolerance to ACE inhibitors. Intolerance was defined as discontinuation of ACE-inhibitor treatment because of one or more of the following adverse effects: cough, symptomatic hypotension, azotaemia, hyperkalaemia, taste disturbance, gastrointestinal upset, or rash. Investigators were encouraged to start β-blocker therapy and titrate dosing to a maximum, whenever possible. Exclusion criteria were: pregnancy or lactation; known intolerance to ARBs; systolic arterial blood pressure less than 90 mm Hg; haemodynamically significant stenotic valvular heart disease; active myocarditis; active pericarditis; planned heart transplantation within 6 months; coronary angioplasty, coronary artery bypass graft surgery, acute myocardial infarction, unstable angina pectoris, cerebrovascular accident, or transient ischaemic attack within the previous 12 weeks; documented or suspected significant renal artery stenosis; contraindication to a vasodilator; life-limiting disease other than heart failure; mental or legal incapacitation; drug or alcohol misuse within the previous 2 years; participation in any investigative drug trial in the previous 4 weeks; serum creatinine greater than 220 μmol/L; serum potassium less than 3·5 mmol/L or greater than 5·7 mmol/L; hepatic enzymes of more than three times the normal range; and haemoglobin less than 6·2 mmol/L.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee or institutional review board of every site. All patients provided their written informed consent before randomisation.

Randomisation and masking

Before randomisation, patients not already receiving an ARB were titrated onto losartan from 12·5 mg daily to 25 mg daily over 2 weeks. For patients already receiving an ARB, their prescription was discontinued, and investigators had the option of starting open-label losartan 25 mg daily for 1 week or randomly assigning the patient directly.

Randomisation was stratified by clinical centre and presence or absence of β-blocker therapy. Within each stratum, patients were randomly assigned to the 150 mg (up-titrated from 50 mg daily over a 3-week period) and 50 mg doses of losartan, with a 1:1 allocation with block randomisation (block size of four). During and after up-titration (or mock titration), every patient received two pills daily: one containing active losartan 50 mg and one containing additional losartan or placebo to achieve the targeted dose. All patients and investigators were masked to treatment assignment. Patients were assessed during titration (weeks 0, 1, 2, and 3 after randomisation) and after dose stabilisation (months 1, 2, 4, 6, 9, and 12), with subsequent monitoring every 6 months until study completion. Serum electrolytes and creatinine were measured at months 1, 4, 9, and 12 and at every 6-month visit thereafter. The blinded treatments were prepackaged with unique allocation numbers and distributed to the clinical sites to be used in order. Although investigators knew the next allocation number to be used, they were not aware of the contents of the double-blind drug.

This trial was overseen by the Steering Committee, whose members were masked throughout. The safety and conduct of the study were monitored by an independent Data and Safety Monitoring Board (DSMB). A statistician (employed by the sponsor, but responsible only to the DSMB) and the DSMB members were unmasked before trial completion.

Study outcomes

The primary endpoint was a composite of death or admission for heart failure. Admission for heart failure was defined as a minimum of 24 h inpatient admission or overnight stay to any health-care facility, with the primary cause being treatment of worsening heart failure and during which an additional diuretic drug, intravenous or oral nitrate, or intravenous inotropic agent was given. The primary hypothesis was that treatment with losartan 150 mg daily would be superior to losartan 50 mg daily, with regard to the primary

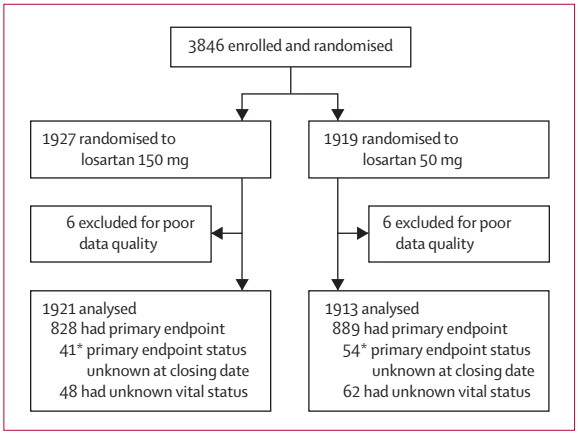
3846 enrolled and randomised
1927 randomised to losartan 150 mg
1919 randomised to losartan 50 mg
6 excluded for poor data quality
6 excluded for poor data quality
1921 analysed
828 had primary endpoint
41* primary endpoint status unknown at closing date
48 had unknown vital status
1913 analysed
889 had primary endpoint
54* primary endpoint status unknown at closing date
62 had unknown vital status

Figure 1: **Trial profile**

*For patients with unknown primary endpoint status, in the 150 mg group, 14 patients were lost to follow-up by 1 year and 26 by 3 years; in the 50 mg group, 15 patients were lost to follow-up by 1 year and 39 by 3 years. The median duration of follow-up for the 41 patients in the 150 mg group who were lost to follow-up for the primary endpoint was 2·0 years (IQR 0·7–3·2) and for the 54 patients in the 50 mg group was 2·0 years (1·0–3·1). Unknown primary endpoint status occurred in 38 of 2429 patients (2%) for Europe, Middle East, and Africa; 33 of 781 patients (4%) for Asia and Pacific; and 24 of 624 patients (4%) for Latin America.

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

	Losartan 150 mg (n=1921)	Losartan 50 mg (n=1913)
General characteristics		
Age (years)	66·0 (56–73)	66·0 (56–72)
Men	1338 (70%)	1353 (71%)
Race		
Asian	427 (22%)	429 (22%)
Black	20 (1%)	15 (1%)
Hispanic	109 (6%)	103 (5%)
White	1156 (60%)	1165 (61%)
Other	209 (11%)	201 (11%)
Clinical history and findings		
Atrial fibrillation	535 (28%)	535 (28%)
Ischaemic heart disease	1221 (64%)	1235 (65%)
Hypertension	1149 (60%)	1143 (60%)
Hyperlipidaemia	1007 (52%)	965 (50%)
Diabetes mellitus	595 (31%)	604 (32%)
NYHA class		
II	1327 (69%)	1330 (70%)
III	583 (30%)	569 (30%)
IV	10 (1%)	12 (1%)
LVEF (%)	33% (28–37)	33% (27–37)
Diastolic blood pressure (mm Hg)	77 (70–80)	77 (70–80)
Systolic blood pressure (mm Hg)	124 (110–140)	125 (112–140)
Pulse rate (beats per min)	71 (64–80)	72 (64–80)
Body-mass index (kg/m²)	26·8 (24·0–30·1)	26·9 (24·1–29·9)
Serum creatinine (μmol/L)	97·2 (80·4–115·8)	97·0 (79·7–114·9)
Serum cholesterol (mmol/L)	4·8 (4·1–5·6)	4·8 (4·1–5·6)
ARB use at screening	1483 (77%)	1457 (76%)
Drug use at randomisation		
Antithrombotic agents/anicoagulants	626 (33%)	602 (32%)
Antiarrhythmics	173 (9%)	224 (12%)
α blockers	34 (2%)	47 (3%)
β blockers	1389 (72%)	1374 (72%)
Calcium-channel blockers	212 (11%)	223 (12%)
Cardiac glycosides	810 (42%)	807 (42%)
Diuretics (excluding aldosterone blockers)	1478 (77%)	1446 (76%)
Aldosterone blockers	728 (38%)	735 (38%)
Salicylic acid and derivates	959 (50%)	999 (52%)
Statins: HMG-CoA reductase inhibitors	754 (39%)	746 (39%)

Data are median (IQR) or number (%). NYHA=New York Heart Association functional class. LVEF=left-ventricular ejection fraction. ARB=angiotensin-receptor blocker. HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A.

Table 1: **Baseline characteristics of patients**

endpoint. The major secondary endpoint was a composite endpoint of death or cardiovascular admission. Additional prespecified outcomes included: death, death or all-cause admission, cardiovascular death, all-cause admission, cardiovascular admission, admission for heart failure, and changes in the severity of heart disease (change in NYHA functional class). The cause of death (cardiovascular or non-cardiovascular) and the primary cause of admission were determined by an Endpoint Classification Committee, whose members were masked to treatment assignment. Adverse events were reported while patients were taking treatment and for 14 days after the end of treatment. Events were coded with the Medical Dictionary for Regulatory Activities (version 12).

Statistical analysis

To provide roughly 95% power at the 4·3% significance level (two-sided, adjusted for interim analysis) to detect a hazard reduction of 16·3% (hazard ratio [HR] 0·837), a target of 1710 patients with primary events was set. The initial sample size and follow-up period that was calculated to obtain the 1710 primary events was based on the assumption that the yearly rate of death or admission for heart failure in the losartan 50 mg group would be similar to that recorded in the ELITE II study (18%).[7] On the basis of an observed overall yearly event rate of 12% (lower than was expected), the target sample size was increased from 3240 to 3656 in April, 2004.

In September, 2008, on the basis of the accumulated number of events that had accrued and the projected event rate for both treatment groups combined, the Steering Committee estimated that the target number of events would be achieved by March 31, 2009, and established that date as the closing date of the trial.

The independent DSMB reviewed interim analyses at least once every year and did formal interim analyses for efficacy after about 50% and 75% of the targeted 1710 adjudicated primary endpoints were detected. An O'Brien-Fleming boundary was used for interim efficacy analyses.

The analyses of the primary and secondary endpoints were by intention to treat. We used time-to-event methods (Kaplan-Meier curves and Cox proportional hazards models) to compare the 150 mg and 50 mg dose groups for major endpoints.[11] Follow-up was censored when patients were lost to follow-up on or before March 31, 2009.

HRs for the 150 mg versus 50 mg dose of losartan were estimated from Cox models, with indicator variables for β-blocker use, region, and treatment group. Geographic regions were defined as: Europe, Middle East, and Africa; Asia and Pacific; and Latin America. We tested the proportional hazards assumption by including an interaction term between the treatment indicator and log-transformed follow-up time. We used Cox models to compare the total number of admissions for multiple heart failure in the two treatment groups.[11]

The primary endpoint was summarised for prespecified subgroups that were defined by demographic and baseline characteristics. The heterogeneity of HR estimates for subgroups was assessed by including an interaction term between treatment and subgroup in expanded Cox models. Subgroup analyses should be interpreted with caution because a significant interaction could be due to chance, since we made no adjustment to type 1 error for the number of subgroups examined.

Changes from baseline in blood pressure, estimated glomerular filtration rate (eGFR) as measured with the

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

	Losartan 150 mg (n=1921)		Losartan 50 mg (n=1913)		HR (95% CI)†	p value†
	Number with event	Rate*	Number with event	Rate*		
All-cause death or heart failure admission	828	11·1	889	12·4	0·90 (0·82–0·99)	0·027
All-cause death or cardiovascular admission	1037	15·6	1085	17·0	0·92 (0·85–1·01)	0·068
All-cause death	635	7·6	665	8·2	0·94 (0·84–1·04)	0·24
Heart failure admission	450	6·0	503	7·0	0·87 (0·76–0·98)	0·025
Cardiovascular admission	762	11·5	826	12·9	0·89 (0·81–0·98)	0·023

*Per 100 patient-years of follow-up. †Hazard ratio (HR) and p value from Cox regression, with region and baseline β-blocker use as covariates.

Table 2: **Hazard ratios for the primary and major secondary endpoints and components**

modification in diet in renal disease equation,[12] and serum potassium are summarised by treatment group by ANCOVA, with baseline covariates corresponding to the measurement of interest, region, and β-blocker use. Proportions of patients at 12 months with serum potassium concentrations greater than 6·0 mmol/L, and serum creatinine concentrations at least twice baseline, were summarised with Mantel-Haenszel χ^2, stratified by region and β-blocker use. Changes in NYHA class from baseline to the end of follow-up were compared with a Wilcoxon rank statistic.

We compared the rates of adverse events and masked treatment discontinuation, overall and for specific reasons, with time-to-event methods. Cox models were used to study baseline predictors of adverse events. In these analyses, treatment discontinuations that occurred within 14 days of death were not counted unless the reason for discontinuation was an adverse event. For the analyses of adverse events, follow-up was censored 14 days after treatment discontinuation. Statistical analyses were done with SAS software (version 9.1).

This study is registered with ClinicalTrials.gov, number NCT00090259.

Role of the funding source

The sponsor of the study was involved in protocol design and undertook study and data management. All final analyses were done by the sponsor and, independently, by a biostatistician at the University of Minnesota (JDN), who is a member of the Steering Committee and who received access to all raw data of the study. The Steering Committee had full responsibility in developing and writing the report, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1927 were randomly assigned to losartan 150 mg daily and 1919 to losartan 50 mg daily (figure 1). Six patients in each group were excluded from the analyses because of poor data quality. The two treatment groups were well balanced at baseline (table 1). At time of screening, ARBs had been prescribed to 1483 (77%) patients in the 150 mg group and to 1457 (76%) in the 50 mg group. Apart from ACE inhibitors, a high proportion of patients were receiving standard therapies for heart failure at time of randomisation, including diuretic drugs, β blockers, and aldosterone blockers (table 1).

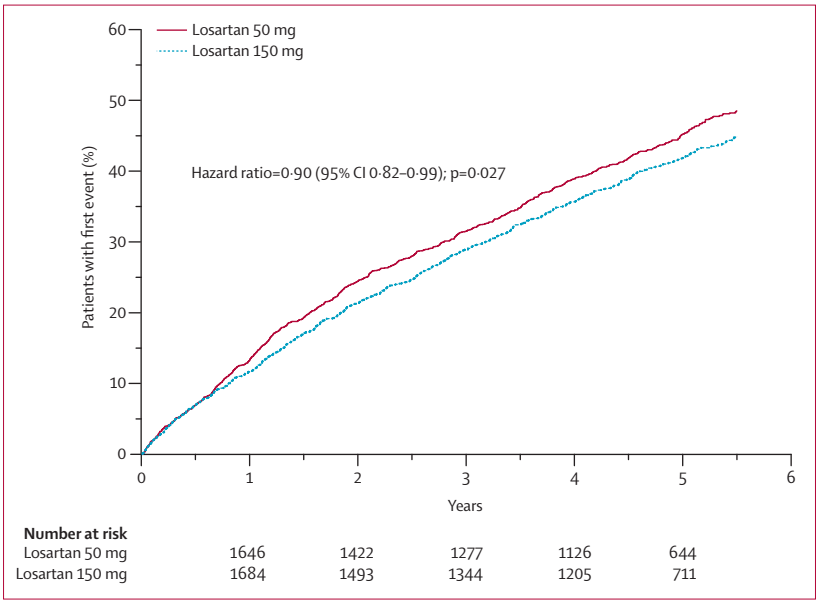

Figure 2: **Kaplan-Meier cumulative event curves for the primary composite endpoint of death or admission for heart failure**

The reported reasons for ACE-inhibitor intolerance were cough (n=3294, 86%), symptomatic hypotension (269, 7%), gastrointestinal upset (193, 5%), rash (97, 3%), taste disturbance (86, 2%), hyperkalaemia (56, 1%), and azotaemia (39, 1%), with some patients having more than one of these symptoms.

Median follow-up was 4·7 years for each treatment group (IQR 3·7–5·5 for losartan 150 mg; 3·4–5·5 for losartan 50 mg). On March 31, 2009, the status for the primary endpoint was unknown for 41 (2%) patients in the 150 mg group and 54 (3%) patients in the 50 mg group, and vital status was unknown for 48 (2%) and 62 (3%) patients, respectively.

During the dose titration period after randomisation, 1808 (94%) patients assigned the 150 mg dose and 1823 (95%) assigned to the 50 mg dose were titrated up to

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

	Losartan 150 mg (n=1921)		Losartan 50 mg (n=1913)		HR (95% CI)†	p value†
	Number with event	Rate*	Number with event	Rate*		
All-cause death or all-cause admission	1237	21·6	1269	22·8	0·95 (0·88–1·03)	0·24
Cardiovascular death	448	5·4	478	5·9	0·92 (0·81–1·05)	0·20
All-cause admission	1079	18·8	1097	19·7	0·96 (0·89–1·05)	0·38
Cardiovascular death or cardiovascular admission	942	14·2	1003	15·7	0·91 (0·83–0·99)	0·034
Cardiovascular death or heart failure admission	698	9·3	771	10·7	0·88 (0·79–0·97)	0·011

*Per 100 patient-years of follow-up. †Hazard ratio (HR) and p value from Cox regression, with region and baseline β-blocker use as covariates.

Table 3: **Hazard ratios for other outcomes**

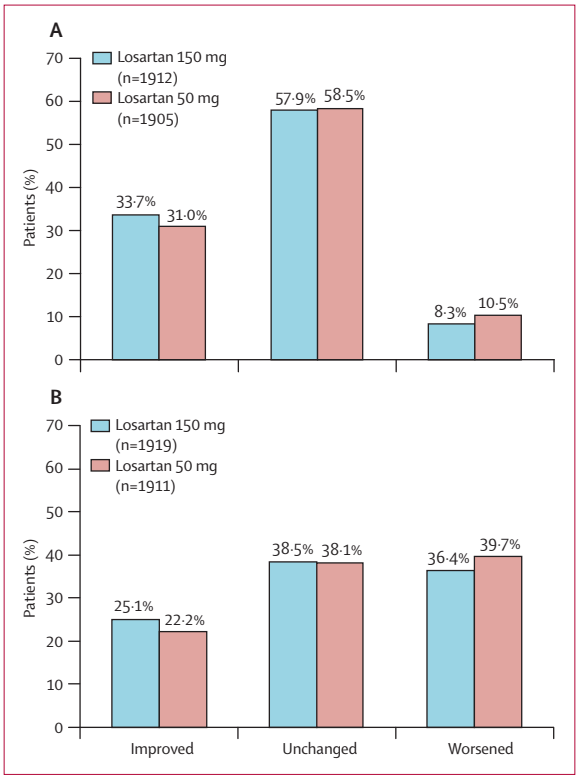

Figure 3: **Changes in New York Heart Association functional class, from baseline to last available data by treatment group, without (A) and with (B) imputation of worsening for patients who died**

p=0·015 for (A) and p=0·013 for (B) for difference between group, based on Wilcoxon Rank Sum test.

the 150 mg dose, or mock 150 mg dose, and remained at this dose for a minimum of 30 days. From the time of follow-up to the time of a primary endpoint or study end, the mean daily losartan doses administered were 129 mg (SD 39) for the 150 mg group and 46 mg (11) for the 50 mg treatment group.

Table 2 summarises results for the primary and secondary outcome endpoints and their components. Losartan 150 mg daily significantly reduced the rate of the primary endpoint compared with losartan 50 mg (table 2). 828 (43%) patients in the 150 mg group and 889 (46%) in the 50 mg group died or were admitted for heart failure (HR 0·90, 95% CI 0·82–0·99; p=0·027). The HR did not vary significantly during follow-up (p=0·93 for proportional hazards). Kaplan-Meier estimates of the cumulative percentage developing this composite endpoint were 11·7% after 12 month, 21·4% after 24 months, 28·9% after 36 months, and 35·7% after 48 months in the 150 mg group, and 13·3%, 24·4%, 31·5%, and 38·9%, respectively, in the 50 mg group (figure 2). On the basis of Kaplan-Meier estimates at 4 years, treating patients with the 150 mg dose instead of the 50 mg dose would result in one additional patient without the primary event at 4 years for every 31 patients treated.

Each of the components of the primary composite endpoint directionally contributed to the overall result (table 2). The most common causes of death were sudden cardiac death, accounting for 37·0% (n=481) of total deaths (234 [37%] in 150 mg group *vs* 247 [37%] in 50 mg group), and death due to progressive heart failure, accounting for 24·2% (n=314) of total deaths (151 [24%] *vs* 163 [25%]). 450 patients had 884 heart failure admissions in the 150 mg group, as compared with the 50 mg group, in which 503 patients had 966 heart failure admissions (p=0·026 for difference in the total number of heart failure admissions between groups).

The secondary endpoint of death or cardiovascular admission occurred in 1037 (54%) patients in the 150 mg group and in 1085 (57%) in the 50 mg group (HR 0·92, 95% CI 0·85–1·01; p=0·068). Table 3 lists results for the additional prespecified endpoints. For every outcome, HRs favoured the 150 mg dose; rates differed significantly for cardiovascular death or cardiovascular admission and for cardiovascular death or heart failure admission (table 3). Compared with the 50 mg group, losartan 150 mg daily improved the distribution of changes in NYHA classes, as measured at last follow-up, compared with baseline, without (p=0·015 between groups) or with (p=0·013) imputation of worsening for patients who died (figure 3).

With one exception, comparisons for prespecified subgroups showed results that were similar to the overall finding (figure 4). We noted a significant treatment-by-subgroup interaction for the primary endpoint for the subgroup based on the presence of a

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

history of hypertension (p=0·01; figure 4). Patients without a history of hypertension had greater treatment benefit with losartan 150 mg daily, compared with losartan 50 mg daily, than did those with a history of hypertension (figure 4).

At 6 months, systolic and diastolic blood pressure fell in both treatment groups from 126/76 mm Hg at baseline. Mean changes were –2·2 mm Hg (SE 0·40) for systolic and –2·1 mm Hg (0·24) for diastolic blood pressure in the 150 mg group and –0·8 mm Hg (0·39) and –0·9 mm Hg (0·24), respectively, in the 50 mg group (p=0·008 and p<0·0001 for between-group difference in systolic and diastolic blood pressure, respectively). Heart rate did not change significantly in either treatment group from the mean baseline value of 73 beats per min. Mean change was –0·11 beats per min (0·25) in the 150 mg group and 0·02 beats per min (0·25) in the 50 mg group (p=0·68 for difference).

At 12 months, serum potassium increased by a mean of 0·02 mmol/L (SE 0·01) in the 150 mg group and decreased by 0·01 mmol/L (0·01) in the 50 mg group (p=0·03 between groups). Serum potassium concentrations were 6·0 mmol/L or greater in 20 (1%) patients in the 150 mg group and in 14 (1%) in the 50 mg group (p=0·32). eGFR was 6·1 mL/min/1·73 m² (SE 0·55) lower at 12 months than at baseline for the 150 mg group and 1·9 mL/min/1·73 m² (0·55) lower for the 50 mg group (p<0·0001 between groups). At 12 months, serum creatinine at least doubled from baseline in 19 (1%) patients in the 150 mg group and nine (<1%) in the 50 mg group (p=0·06).

544 (28%) patients in the 150 mg group and 522 (27%) in the 50 mg group discontinued masked treatment (p=0·67 for difference). Fewer than 10% of patients in each group had discontinued treatment by 12 months. Kaplan-Meier estimates of the cumulative percentage of patients remaining on study treatment at 48 months were 76·6% for the 150 mg group and 75·7% for the 50 mg group. 429 (22%) patients in the 150 mg group and 409 (21%) in the 50 mg group discontinued treatment before first hospital admission for heart failure (p=0·76). 148 patients in the 150 mg group and 133 in the 50 mg group discontinued masked medication because of an adverse event (p=0·44; table 4).

The adverse events of hyperkalaemia, hypotension, and renal impairment, as defined by investigators, occurred more commonly in the 150 mg group than the 50 mg group (table 4). On the basis of Cox regression analysis, each of these adverse events was more likely to occur in patients who listed the adverse event as a reason for ACE-inhibitor intolerance at entry, in older patients, and in those taking aldosterone blockers (data not shown). Renal impairment was the adverse event that led to drug discontinuation most often (table 4). Angioedema occurred in six patients in the 150 mg group and in none in the 50 mg group. The event resulted in study drug discontinuation in four of the six patients. None of the events precipitated admission, and symptoms resolved in all patients between 1 day and 3 months after onset.

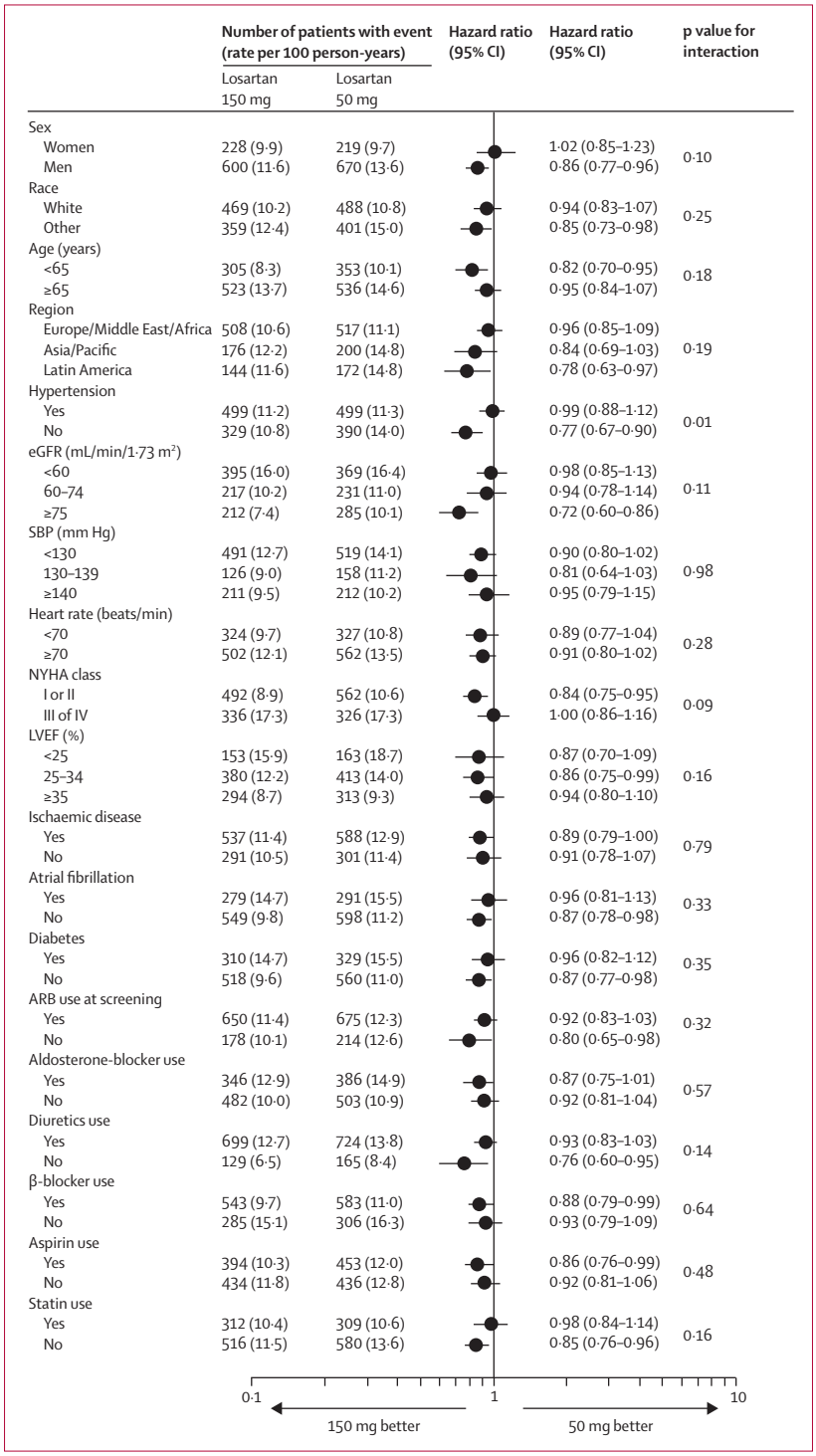

Figure 4: **Hazard ratios for death or admission for heart failure, according to baseline subgroups**
Treatment by subgroup interaction p value is for trend. eGFR=estimated glomerular filtration rate. SBP=systolic blood pressure. NYHA=New York Heart Association. LVEF=left-ventricular ejection fraction. ARB=angiotensin-receptor blocker.

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

	Adverse events*				p value†	Adverse events* with discontinuation‡				p value†
	Losartan 150 mg		Losartan 50 mg			Losartan 150 mg		Losartan 50 mg		
	Number with event	Rate§	Number with event	Rate§		Number with event	Rate§	Number with event	Rate§	
Hyperkalaemia (or increased potassium)	195	2·79	131	1·87	0·0004	9	0·12	4	0·05	0·20
Hypotension	203	2·92	145	2·07	0·002	19	0·26	16	0·22	0·65
Renal impairment¶ (or increased creatinine)	454	7·12	317	4·73	<0·0001	48	0·65	36	0·49	0·22
Angioedema	6	0·08	0	0·0	0·03	4	0·05	0	0·00	0·12
Total adverse events with discontinuation‡	..	..	..	..	..	148	1·99	133	1·83	0·44

*As reported by investigators, events occurring on study drug or within 14 days of discontinuing study drug. †p value from Cox regression, with region and baseline β-blocker use as covariates. Fisher's exact test is given for angioedema. ‡Permanent discontinuations from study drug. §Rate per 100 person-years. ¶Includes the following terms preferred by the Medical Dictionary for Regulatory Activities: renal failure, renal failure acute, renal failure chronic, renal impairment, and pre-renal failure.

Table 4: **Selected adverse events and adverse events with discontinuation**

Discussion

Our findings show that, for patients with heart failure and reduced LVEF who are ACE-inhibitor intolerant, losartan 150 mg daily is superior to 50 mg daily with respect to the composite outcome of death or admission for heart failure. Results for prespecified secondary outcomes and changes in NYHA class lend support to the greater efficacy of the 150 mg dose than of the 50 mg dose. Although more patients receiving the 150 mg dose than the 50 mg dose had hyperkalaemia, hypotension, and renal impairment, these adverse events infrequently led to discontinuation of masked treatment. These findings suggest that increased doses of an ARB are needed to achieve the maximum benefit for clinical outcomes and symptoms related to heart failure in this population.

The most definitive evidence so far of a favourable effect of ARBs on cardiovascular outcomes in patients with chronic heart failure, in the absence of concomitant ACE-inhibitor treatment, is from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Alternative trial.[13] That study showed that candesartan 32 mg daily, compared with placebo, reduced the rate of cardiovascular death or heart failure admission by 23% in patients who were intolerant to ACE inhibitors and who had heart failure and reduced LVEF. Two additional studies[1,6] have shown additive benefit of an ARB in similar patient populations already receiving background therapy that included ACE inhibitors and β blockers. Investigators of the Valsartan Heart Failure Trial (Val-HeFT)[1] reported that addition of valsartan 160 mg twice daily (mean achieved dose 254 mg daily) reduced the rate of admission for heart failure, although they noted no overall effect on mortality. In the subgroup (7% of the population) in whom ACE inhibitors were not given, valsartan treatment was associated with a 33% reduction in mortality and a 53% reduction in heart failure admission.[4] The CHARM-Added trial[6] recorded a 15% reduction in the rate of cardiovascular death or heart failure admission with candesartan 32 mg daily (mean achieved dose at 6 months 24 mg daily) in a population already treated with ACE inhibitors.

With examination of the HEAAL primary combined endpoint of all-cause death or heart failure admission, CHARM-Added showed that high-dose candesartan, added to background ACE inhibition, had a magnitude of effect (HR 0·87, 95% CI 0·78–0·98) similar to the recorded difference between the two losartan doses in HEAAL. Taken together, results of CHARM-Added and HEAAL make a strong case for the value of incremental inhibition of the renin-angiotensin system. The present findings suggest that similar benefit could be achieved by increasing the dose of a particular agent, rather than by addition of an additional class of agent, although future studies are needed to directly test this hypothesis.

Several factors contributed to the hypothesis that increased ARB dose improved heart failure outcomes. ELITE II enrolled 3152 patients, with a minimum age of 60 years (mean age 71 years), with NYHA class II–IV heart failure and LVEF 40% or less.[7] Although the primary endpoint in ELITE II was not powered to establish the non-inferiority of losartan with captopril in the dose given, secondary outcome endpoints and measures of symptom severity of clinical heart failure were similar between the two treatment groups.[14] Doses of losartan of up to 100 mg daily improved cardiovascular and renal outcomes in large outcome studies of hypertension with left-ventricular hypertrophy[15] and of diabetic nephropathy,[16] respectively. A post-hoc analysis of patients with diabetes from these two studies showed reduction in admissions for heart failure.[17] In the setting of heart failure after acute myocardial infarction, the high dose of valsartan (target 320 mg daily, achieved 247 mg daily) used in the VALIANT trial[3] was non-inferior to captopril (target 150 mg daily, achieved 117 mg daily) for clinical outcomes, whereas the dose of losartan (target 50 mg daily, achieved 45 mg daily) used in the OPTIMAAL[18] trial did not achieve non-inferiority to the same target dose of captopril (target 150 mg daily, achieved 132 mg daily). Findings from these studies, coupled with the favourable effects in Val-HeFT[1] and CHARM,[2,6,13] suggest that a high

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

ARB dose drives improved clinical outcomes; however, the relation between ARB dose and treatment effect remains uncertain.

The Assessment of Treatment with Lisinopril and Survival (ATLAS) study[19] investigated the relative effect of different ACE-inhibitor doses, comparing lisinopril 32·5–35 mg daily versus lisinopril 2·5–5·0 mg daily. Investigators of this study reported a 12% reduction in the risk of the secondary endpoint of death or admission (p=0·002) and a 15% reduction in the risk of death or heart failure admission (a post-hoc endpoint). These findings also lend support to the value of incremental inhibition of the renin-angiotensin system, although the spread between doses chosen was very wide, and the primary endpoint of death did not differ significantly between groups. An additional study[20] comparing two doses of enalapril was underpowered to show an outcome treatment difference.

In HEAAL, we chose to examine the effects of losartan 150 mg daily—a dose that is known to have an acceptable safety and tolerability profile,[21] while being substantially higher than the 50 mg daily dose used in ELITE II. Evidence exists for incremental AT_1 receptor inhibition[22] associated with increases in plasma renin activity and in circulating angiotensin-II concentrations in patients with heart failure,[8] with increased dose across this range.

Our findings lend support to titration to the high ARB doses used in clinical trials, unless limited by adverse effect, to achieve improved clinical outcomes in patients with heart failure and reduced LVEF. Although the 10% primary endpoint hazard reduction that we recorded was somewhat less than that noted in other heart failure trials, this treatment effect is relative to a dose of losartan that is known to achieve substantial AT_1 receptor antagonism, rather than to placebo. The 150 mg dose of losartan achieved a significant 13% reduction in admission for heart failure compared with 50 mg daily. This incremental benefit of losartan 150 mg daily compared with 50 mg daily occurred with a substantially higher percentage of patients receiving background treatment with β blockers (72%) compared with ELITE II (22%),[7] Val-HeFT (38%),[1] CHARM-Alternative (55%),[13] and CHARM-Added (55%).[6]

The outcome benefits of losartan 150 mg daily have to be weighed against the several types of adverse effects that we detected with increased frequency. The rates of hypotension, hyperkalaemia, and renal failure were greater with losartan 150 mg daily than with losartan 50 mg daily. However, the overall rates and clinical relevance of these events were small, as shown by the infrequent discontinuation of study drug, which occurred with similar frequency to that recorded in previous investigations of ARBs.[1–3,6,7,18] These findings should be considered in the context that 77% of patients were treated with ARBs before randomisation and that a run-in period was used, probably resulting in the enrolment of patients who would better tolerate high doses of losartan over long-term follow-up. Blood pressure, serum electrolytes, and renal function should be monitored carefully during ARB up-titration, and the clinical implications of changes in any of these variables should be weighed against the potential outcome benefits that are achievable with an increased ARB dose. Previous studies have suggested that the incidence of angioedema is very low.[13] Our findings suggest a small but finite and dose-related risk of angioedema with losartan.

Several limitations of HEAAL should be considered. We studied only patients who were intolerant to ACE inhibitors. Although there is no evidence to lend support to differential benefit of ARBs in patients who are able to tolerate ACE inhibitors, compared with those who are not, we cannot be certain whether our findings would be reproduced in patients being treated de novo, compared with those known to be intolerant of ACE inhibitors. However, we noted that patients having hypotension, hyperkalaemia, or azotaemia during treatment with an ACE inhibitor were more likely to have that effect during losartan treatment, suggesting that a population without previous ACE inhibitor intolerance might have tolerated the increased ARB dose more favourably. Since the effect of losartan 50 mg daily on outcomes related to heart failure has never been tested relative to placebo, direct estimations of the magnitude of benefit of losartan 150 mg daily cannot be made from our results. Finally, although our findings accord with the view that increased inhibition of the renin-angiotensin system achieves incremental clinical benefit, we cannot establish whether greater benefit might have been achievable by combining losartan with an ACE inhibitor, rather than further increasing the losartan dose.

Contributors

All Steering Committee members (MAK, PAP-W, JDN, KD, HD, MK, FAM, GAJR) contributed to and approved the design of the study. This group oversaw the conduct of the trial throughout. KD, MK, WM, RDS, and SG were involved in data collection. Data were analysed independently by JDN and WM, in continuous direct discussion and consultation with MAK. All authors, apart from PAP-W and HD, who both died in 2009, had full access to the data and contributed to data review and analysis. MAK and RDS did the literature search. MAK oversaw the entire process of generating the report. He wrote the initial draft, coordinated all suggestions and edits, maintained responsibility throughout, and made final decisions on all aspects of the submitted manuscript. All authors apart from PAP-W and HD participated in reviewing and editing the report. No one other than the authors was involved in writing this report.

HEAAL committees

Steering Committee Marvin A Konstam (co-chair), Philip A Poole-Wilson* (co-chair), Kenneth Dickstein, Helmut Drexler*, Michel Komajda, Felipe A Martinez, James D Neaton, Gunter A J Riegger (*deceased). *Independent Data Safety Monitoring Board* Henry Dargie (chair), Gary Francis, Wolfgang Kuebler, Hans Wedel, Faiez Zannad, Tom Loeys. *Endpoint Adjudication Committee* Jordi Soler-Soler, Gerd Hassenfuss, Matti Romo, Constantina Manes, J S R Gibbs. *Merck Coordination Team* Steve Justice, Diane Delaplace, Maria Vala, Rachel Capece, Goeff Tansley, William Malbecq, Ronald D Smith.

Investigators

Belgium F Charlier, P H Henry, J Vanhaecke, W Van Mieghem; *Brazil* G Feitosa Soares, S Rassi; *Chile* F Lanas, A I Puelma Paredes; *China* N S Cai, J Z Chen, Y Chen, W H Fan, J Guo, D Hu, D Huang, J Huang, Y Ke, Y Li, Y Liao, G Lu, H Ma, L Wang, M Wei, S Wu, Y Zhang, X Zheng, S Zhou, W Zhu; *Colombia* M Garcia, C J Jaramillo, M A Urina,

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

S Velez; *Croatia* M Padovan, D Plavljanic, D Pocanic, A Smalcelj; *Egypt* O S Awwad, M A Taher, A M Zaki; *France* (Coordinating Investigator: M Komajda) J-P Bassand, N Benazza, K Bouchlaghem, A Boudhane, Z Chati, D Coisne, F Delahaye, T Denolle, T Drawin, J-J Dujardin, F Funck, P Gibelin, L Hittinger, E, Khaldi, M Komajda, J-M Mallion, M Martelet, J-N Trochu; *Germany* V Adelberger, J Adler, C Albrecht, A Al-Zoebi, M Baar, G Bohm, D Boscher, H Bouzo, A Brattström, M Deissner, R Dichmann, K Droese, M Dursch, H-H Ebert, E Erdmann, H M Frick, J Gadow, J Gartner, M Guha, H Gunther, N Hassler, G Haustein, S Heinemann, G-U Heinz, R Henke, A Himpel-Bonninghoff, H Hohensee, T Horacek, N Jahnke, P Kindermann, C Klein, H Klepzig, I Kordish, H-G Krezdorn, R Lange, M Leicht, S Mobius-Winkler, M Oelker, U Overhoff, B Pieske, N Proskynitopolous, A J Rouwen, H Sachs, T Schafer, U Schax, E Schmidt, E M Schmidt-Rauch, A Schreckenberg, H Y Sohn, S G Spitzer, H D Stahl, C Steffens, R Stohring, A Tammen, S Troger, W Turk, M Unverdorben, J Walter, M Weissbrodt, G Weppner, J Wunderlich; *Greece* S Adamopoulos, E Adamopoulou, D Kremastinos, A Manolis, I Nanas; *Hong Kong* H F Tse, C M Yu; *Italy* G Ambrosio, A Branzi, C Brunelli, G D'Angelo, L Deicas, L Di Cioccio, R Ferrari, V Grassi, A Grieco, V Inserra, G Lembo, R Pedrinelli, F Purrello, L Tavazzi, P Terrosu, B Trimarco, M Volpe, S M Zuccaro; *Korea* E-S Jeon, J-J Kim; *Lebanon* A Abchee, R Kassab, A Rebeiz; *Malaysia* D S P Chew, K H Sim, Z Yusof; *Mexico* M Marquez, E Meaney; *Morocco* M Benomar, J-E Srairi, R EL Akil, L Bouchara; *Netherlands* B J van den Berg, P H van der Burgh, P A R De Milliano, R M M Gevers, E J A M Gobel, G C M Linssen, J A Kragten, R F Veldkamp, D J van Veldhuisen, L J van Woerkens; *Norway* E Aaser, K Dickstein, L Gullestad, K Hofsøy, T Hole, J E Otterstad, A Skogsholm, A Westheim; *Peru* M E Horna Noriega, J J Lema Osores, F Medina, L Segura; *Philippines* M T Abola, A M Dans, D Morales, E Ramos, G Rogelio, R Sy; *Poland* J Adamus, J Bakun, Z Gaciong, S Kocon, L Kubik, A Rynkiewicz, K Sokolowski, D Wojciechowski; *Russian Federation* G P Aroutiounov, V Y Mareyev, B A Sidorenko; *Singapore* B W K Kwok; *Slovenia* (Coordinating Investigator: I Keber) I Keber, N Ruzic Medvescek, F Skrabl Mocnik; *South Africa* A F Doubell, E Lloyd, J D Marx, D P Naidoo; *Spain* L A Alonso Pulpon, M P Anguita-Sanchez, F Arnalich Fernandez, V Barrios-Alonso, J R Berrazueta Fernandez, V Bertomeu-Martinez, E De Teresa Galvan, A Espolitas Santos, I Ferreira-Montero, A del Rio Ligorit, E Galve-Basilio, M A Gomez-Sanchez, J R Gonzalez-Juanatey, C Martin Luengo, A Melero-Pita, R Munoz-Aguilera, V Ramos Poyedo, M A Rodriguez-Garcia, M E Roig Minguell, L Sainz-Cusi, A Salvador Sanz, B Sevilla Toral, M Valdes Chavarri, V Valle Tudela; *Taiwan* C-H Chen, H-T Chou, J-Y C Hou, C-P Liu, D Wu; *Turkey* N Caglar, S Kes, N Koylan, O Kozan; *UK* M Brack, C Brookes, D Bruce, J Davies, F Dunn, D P Dutka, N Gough, P Groves, I Haq, H H Kadr, P J Keeling, C Kyle, G W Lloyd, R J MacFadyen, J McLay, A Mehrzad, D L Murdoch, M Petrie, S G Ray, B Saeed, S Saltissi, R Senior, I B Squire, J Tilley, C Travill, J Walsh, I Wiles, I Wilson, A Wijnberg.

Conflicts of interest

MAK, JDN, KD, HD, MK, FAM, GAJR, and PAP-W have served as consultants to, or received research grants from, Merck. WM, RDS, and SG are current or former employees of Merck and have an equity interest in the company.

Acknowledgments

This study was supported by Merck & Co, Inc. Whitehouse Station, NJ, USA. We thank our investigators and their patients for their participation, Brenda Vanslembrouck for coordinating clinical drug supply, and Rachid Massaad and Deborah Wentworth for statistical analyses. The authors wish to dedicate this report to the memories of Prof Philip A Poole-Wilson and Prof Helmut Drexler.

References

1 Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667–75.

2 Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; **362:** 759–66.

3 Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349:** 1893–906.

4 Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002; **40:** 1414–21.

5 Krum H, Carson P, Farsang C, et al. Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. *Eur J Heart Fail* 2004; **6:** 937–45.

6 McMurray JJV, Östergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.

7 Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the losartan heart failure survival study ELITE II. *Lancet* 2000; **355:** 1582–87.

8 Gottlieb SS, Dickstein K, Fleck E, et al. Hemodynamic and neurohormonal effects of the angiotensin II antagonist losartan in patients with congestive heart failure. *Circulation* 1993; **88:** 1602–09.

9 Dzau VJ, Sasamura H, Hein L. Heterogeneity of angiotensin synthetic pathways and receptor subtypes—physiological and pharmacological implications. *J Hypertens* 1993; **11:** S13–18.

10 Konstam MA, Poole-Wilson PA, Dickstein K, et al. Design of the Heart failure Endpoint evaluation of AII-Antagonist Losartan (HEAAL) study in patients intolerant to ACE-inhibitor. *Eur J Heart Fail* 2008; **10:** 899–906.

11 Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer-Verlag, 2000.

12 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130:** 461–70.

13 Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362:** 772–76.

14 Konstam MA, Neaton JD, Poole-Wilson PA, et al. Comparison of losartan and captopril on heart failure-related outcomes and symptoms from the losartan heart failure survival study (ELITE II). *Am Heart J* 2005; **150:** 123–31.

15 Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 995–1003.

16 Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345:** 861–69.

17 Carr AA, Kowey PR, Devereux RB, et al. Hospitalizations for new heart failure among subjects with diabetes mellitus in the RENAAL and LIFE studies. *Am J Cardiol* 2005; **96:** 1530–36.

18 Dickstein K, Kjekshus J, the OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002; **360:** 752–60.

19 Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; **100:** 2312–18.

20 Nanas JN, Alexopoulos G, Anastasiou-Nana MI, et al. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. High Enalapril Dose Study Group. *J Am Coll Cardiol* 2000; **36:** 2090–95,

21 Weber M. Clinical safety and tolerability of losartan. *Clin Therap* 1997; **19:** 604–16.

22 Regitz-Zagrosek V, Neuss M, Fleck E. Effects of angiotensin receptor antagonists in heart failure: clinical and experimental aspectes. *Eur Heart J* 1995; **16** (suppl N)**:** 86–91.

Descargado para Anonymous User (n/a) en Autonomous University of Bucaramanga de ClinicalKey.es por Elsevier en septiembre 20, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.